REMARKS

In response to an *Election Requirement* mailed 29 May 2007, Applicants elected the Group I claims (i.e., 1-41 and 140-143), and the Group II-XII claims (i.e., 42-139) were withdrawn pursuant to 37 C.F.R. §1.142(b). In a previous response, Applicants traversed that requirement relative to the Group II claims (i.e., 42-85) but the Examiner maintained the requirement over those as well as the claims of the other unelected groups III-XII.

Claim 1 has been amended to further highlight its patentability over the prior art of record. Applicants also present arguments below in further support of the patentability of all claims in view of the rejections contained within the pending Office Action.

Claims 1-41 And 140-143 Stand Rejected Under 35 U.S.C. §103(a)

Claims 1-41 and 140-143 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent 6,468,506 to *Rössling et al.* in view of U.S. Patent 5,885,216 to *Evans, III et al.* and further in view of U.S. Patent 6,231,513 to *Daum et al.* or International Publication WO96/40282 to *Quay et al.* In particular, the Examiner stated that:

> 5. Rossling et al. (US 6,468,506Bl) discloses an apparatus for the production of gaseous microparticles for ultrasound diagnosis and the process for the production of gaseous microparticles (abstract; column 1, lines 8-9). The process for the production of gaseous microparticles involved pumping in gas into a surface-active substance solution and mixing with a stirring mechanism (column 2, lines 35-44). An alternative method or the production of gaseous microparticles involves spraying the solution via a nozzle into a column of gas into a column of gas (column 3, lines 25-29). The size of the resulting particles may be controlled by the nozzle size, shape, type as well as the working pressure and temperature in the column (column 3, lines 49-51). Figure 1 shows the apparatus for the production of gaseous microparticles. The apparatus includes a tank which may be filled with gas via a valve and line. The pump moves the solution from a tank via nozzle into a line, heat exchanger and column of gas, etc. Rossling et al. does not disclose a medium delivery system for direct injection into a patient or the production of microbubbles via ultrasound or the introduction of solid particles.
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> 6. .Evans, III et al. (US 5,885,216) discloses an apparatus for the injection of a contrast medium into a patient (column 3, lines 4-8). The apparatus comprises an electronic control system (column 5, lines 63-66) which provides for proper fluid flows according to the instructions of the operator and gets information on the contents of the bulk reservoirs (column 3, lines 57-59). Sensors are used to inform the controller system when the container is empty or for fluid assurance to prevent the problem of air embolism (column 3, lines 64+; column 4, lines 6-9). A metering pump (peristaltic pump) is used to draw

contrast agent from the reservoir (column 4, lines 30-35), then a mixer is used to mix the fluids and a concentration monitor is used to provide feedback on the density, concentration, etc. (column 4, lines 44-62). A "sterilizing filter" is used to provide for sterile fluid coming out of the pump and to prevent migration of any bacteria from the patient into the pump and a spring-loaded ball valve is used to help prevent cross-contamination (column 4, lines 64+; column 5, lines 38-46).

7. Daum et al. (US 6,231,513) discloses the use of piezoelectric ultrasound for the preparation of gas-filled microbubbles used for ultrasound diagnosis. (column 4, lines 10-24). The apparatus includes passing a gas through the a porous matrix via microholes (column 3, lines 1-28).

8. Quay et al. (WO 96140282) discloses the enhance production of gaseous microbubbles via the introduction of solid particles (p6, lines 7-12; p8, lines 7-25).

9. At the time of the invention it would be obvious to one ordinarily skilled in the art to utilize/try the microparticles prepared by the apparatus of Rossling et al. with the injector system of Evans, III et al. for direct administration of the contrast agent to a patient. Both disclosures are drawn to the same products, such contrast agents having the same utility, thus the results for combining would lead to predictable results. It would also be obvious to generate the microparticles via nucleation or piezoelectric ultrasound as they are all known techniques in the art. One would have a reasonable expectation of success for introducing a plurality of gases via inlets to vary/enhance the microbubble composition.

Applicants respectfully submit that independent claims 1 and 140, and their dependents 2-41 and 141-143, respectively, are not rendered obvious by the combined teachings of *Rŏssling et al.*, *Evans, III et al.* and *Daum et al.* or *Quay et al.* As to claim 1, this is true even before the amendment of the claim herein. Nevertheless, as amended above, claim 1 now more clearly recites "[a] *system for administering into a patient a medium in which* [the] *bubbles therein are created according to the demands of* [*the*] *medical procedure*" that is being performed on the patient. The last paragraph of the claim provides that the "*controller* [of the system controls the] *operation of* [the] *system real-time so that the bubbles created by* [the] *bubble generator are generated according to the demands of the medical procedure and then administered within the medium to the patient.*"

The *Rŏssling et al.* patent does not teach such a system. Instead, it discloses a method of making dried spherically-shaped microparticles in which a gas (e.g., air) is enclosed. (col. 2, lines 1-2; col. 9, line 65) The last step of the method involves removing the dried microparticles from column 19, as shown in Figure 1. (col. 5, lines 28-33; col. 10, lines 32-36) The dried micro-particulate product is then destined for packaging and shipment for later use at sites where ultrasound imaging procedures can be performed. Once delivered to such a site, the dried microparticles can then be suspended in a

pharmaceutically acceptable suspension medium (e.g., water) to create the contrast agent. (col. 3, lines 60-67) The resulting contrast agent is then ready for injection into a patient to enhance the images obtained during an ultrasound imaging procedure.

Although the *Rössling et al.* reference teaches a method of making dried microparticles, it fails to disclose a system for administering into a patient a medium in which the bubbles therein are created according to the demands of the medical procedure. More specifically, it contains no teaching of a controller that controls operation of the system real-time so that the bubbles created by the bubble generator are generated according to the demands of the medical (e.g., imaging) procedure to which the patient is subjected. As the Examiner has noted, the *Rössling et al.* patent clearly does not disclose such a system, as it only teaches the making of dried microparticles to which water is to be added later for purpose of re-hydrating to create a bubble-based contrast medium.

The *Evans, III et al.* patent, either alone or in combination with the *Rössling et al.* patent, also does not teach the system claimed in claim 1. Instead, it discloses a process/system that permits contrast of varying concentration to be injected into a patient. More specifically, the system of *Evans, III et al.* includes separate bulk containers 10 and 11 for contrast and diluent, a metering pump 12 and 13 for each bulk container, and a static mixer 20 into which the metering pumps 12 and 13 push the desired amounts of contrast and/or diluent. (col. 4, lines 16-43) In the static mixer 20, the contrast is mixed and diluted to the desired concentration. The resultant medium is then passed through, inter alia, fluid assurance detector 22, pressurization pump 25, sterile filter 26, connector tube 27, 3-way stop cock 30, and then into the patient. (col. 4 ,line 44 - col. 5, line 61) The system also includes an electronic control system (ECS) 35 that obtains data as to the types and amounts of fluid in bulk containers 10 and 11 via scanning of bar codes 10' and 11' or via input by an operator using a user interface. The user interface or electronic interface 36 also allow entry of patient weight and other inputs. The ECS 35 uses these parameters to calculate the total volume and the appropriate

concentration of contrast to be delivered, and the flow rate. (col. 7, lines 27-34) The bottom line is that the *Evans, III et al.* patent teaches only the mixing of contrast to the desired concentration and delivery of same into the patient. (col. 5, lines 60-61; col. 6, lines 38-40)

While the *Evans, III et al.* patent discloses a system for diluting contrast to a desired concentration level and administering same into a patient, it teaches nothing about generation of bubble-based media and control of same (real-time or otherwise) according to the demands of the procedure that the patient is undergoing and into whom it is to be immediately administered/injected. Even if the teachings of *Rössling et al.* could be combined with those of *Evans, III et al.*, at best they would yield a contrast dilution system to which the dried microparticles of *Rössling et al.* would somehow be added. But alas, there is no suggestion whatsoever as to what point in the method of the *Evans, III et al.* the dried microparticles would be added or how they would be processed by the combined system so that a bubble-based contrast agent safe for human use would be created. This is important because the process taught by *Rössling et al.* uses toxic solvent(s) to create the dried microparticles and thus requires their removal from the mixture before the dried microparticles can be obtained therefrom. (col. 3, lines 4-8; col. 10, lines 2-31) Consequently, if the teachings of *Rössling et al.* and *Evans, III et al.* could be combined, they would likely result in a bubble contrast dilution system that would pose a severe health hazard because the toxic solvents might not be completely removed by separator 10 (Id; and Figure 1), or otherwise evaporated from the dried microparticles, before whatever re-hydration process the combined system would employ. No such toxic solvents are employed in the systems taught or claimed by Applicants.

Furthermore, as noted by the Examiner, the size of the dried microparticles created by the method of *Rössling et al.* is entirely dependent on the size, shape and type of nozzle used in their manufacture. (column 3, lines 49-51) Therefore, again, if this teaching could be combined with those of *Evans, III et al.*, it would yield a contrast dilution system in which the bubbles could not be generated

or controlled according to the demands of the medical procedure that the patient is undergoing. This is because any such change in microparticle size would require a different nozzle to be installed in the apparatus of *Rŏssling et al.*, which Figure 1 suggests is an arduous and time-consuming task -- a manual task that is contrary to the real-time control of bubble generation of Applicants' claims. Whatever system the combination of *Rŏssling et al.* and *Evans, III et al.* would yield, it would not produce a system that enables its operation to be controlled real-time so that the bubbles it creates within the medium are generated according to the demands of the medical procedure. In this regard, *Evans, III et al.* in fact teach away from what the Applicants have disclosed and claimed in the present application.

The *Daum et al.* and *Quay et al.* references are likewise inapposite to buttress the pending 35 U.S.C. §103(a) rejection.

The *Daum et al.* patent discloses devices that are inserted into a blood vessel wherein they are used to form microbubbles in the blood for use in ultrasonic imaging procedures. One such device is a needle 20 in whose pointed distal end 21 is housed a beveled porous matrix 23. When the needle 20 is inserted into a vessel, gas passes through the lumen 24 and flows through the porous matrix 23 resulting in the formation of microbubbles in the blood. (col. 3, lines 57-63) Another such device features a needle 101 at the proximal end 103 of which is affixed a piezoelectric ultrasound transmitter 102. In operation, the distal end of needle 101 is inserted into a vessel. Gas from a source thereof then flows via connector 105 through the hollow shaft of needle 101 and into the vessel. While that is happening, ultrasonic waves formed by activation of transmitter 102 causes vibrations that break the flow of the gas into microbubbles within the blood stream. (col. 4, lines 10-23)

The *Quay et al.* publication discloses a method/apparatus for forming a "microbubble-containing solution" and then administering that solution to an animal. (p. 22,lines 4-8; p. 23, lines 1-5 & 13-15) The solution is formed only in bulk volume (Id. & p. 8, lines 6-25), i.e., all at one time, and it is formed

using an activation method, which *Quay et al.* expressly define as only through the use of "a hypobaric force on [the] solution." (p. 5, line 36 - p. 6, line 3) In other words, the apparatus of *Quay et al.* creates bubble-based media only in bulk volume and only in response to the lowering of pressure in the container in which the solution is stored. Consequently, unlike the system recited in the pending claims, the apparatus of *Quay et al.* is not capable of creating, and hence altering the characteristics of, the bubbles on the fly, as the demands of the medical procedure change. The real-time control of Applicants' claimed system over the bubble generator recited in the claims makes this possible.

The *Daum et al.* patent pertains only to creation of bubbles directly within a blood vessel by means of gas injected via a needle. The *Quay et al.* publication pertains only to bulk formation of a bubble contrast medium, which is then injected into the blood stream. Neither employs the feedback necessary to achieve the real-time operational control of the system in such a way so that the contrast medium has bubbles generated therein according the demands of the medical procedure. Such a system, as contemplated by the Applicants' claims, is not within the ambit of either of these prior art references and their combination with *Rŏssling et al.* and *Evans, III et al.* do not yield same.

From the foregoing, it is equally apparent that none of the cited prior art references, either alone or in combination, disclose a system for creating a plurality of differentiable populations of bubbles for use within a medium to be administered into a patient. For this reason, claim 140 and its dependents 141-143 are likewise patentable over the prior art of record.

For the above reasons, Applicants respectfully submit that combined teachings of *Rŏssling et al.*, *Evans, III et al.* and *Daum et al.* or *Quay et al.* do not render obvious the subject matter recited in independent claims 1 and 140 and their dependents 2-41 and 141-143. In view of the foregoing amendments and arguments, Applicants believe that the §103(a) rejections have been overcome.

CONCLUSION

Before entry of this *Amendment And Response*, the present application had forty-five (45) claims pending, two (2) of which independent. Upon entry of this *Amendment And Response*, the application will still contain forty-five (45) claims, two (2) of which independent.

Given the foregoing, Applicants respectfully request withdrawal of the rejections set forth in the Office Action dated 5 November 2007. Applicants believe the application is ready to be allowed. If the Examiner has any questions regarding this *Amendment and Response*, he is invited to call the undersigned at the telephone number listed below.

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I hereby certify that this correspondence is being electronically filed with the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on 5 February 2008.

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